Letter to the Editor

Regulatory Considerations on the Development, Evaluation, and Approval of Therapies in Rheumatoid Arthritis Prevention

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Perhaps the greatest promise of modern medicine is not that we may eventually be able to treat or cure nearly all diseases but rather that we will routinely be able to prevent or significantly delay the phases of disease in which clinically apparent tissue injury and disease occur. An example is the treatment of elevated cholesterol levels to prevent or delay future myocardial infarction. Indeed, in rheumatoid arthritis (RA), several trials are completed or underway that are evaluating the efficacy and safety of pharmacologic interventions to prevent or delay the future development of clinically apparent inflammatory arthritis.[1]

The development of prevention trials in RA, and then implementing findings into routine clinical practice, is a novel area. As such, there is not yet a clear delineation of the acceptance parameters for regulatory success in prevention of this specific disease. RA is a somewhat distinctive disease; however, based on screening and prevention approaches in other diseases such as cardiovascular disease, osteoporosis, and cancer,[2–5] one can identify several guiding principles that can be deemed requirements for developing clinical trials and ultimately gaining approvals for RA therapies from regulatory agencies (eg, US Food and Drug Administration, European Medicines Agency in Europe). Furthermore, these approaches are also useful as a method to gain approval from other stakeholders that would be participating in prevention such as insurance companies and governmental agencies that set guidelines for screening and prevention (eg, United States Preventive Task Force) and governmental agencies that provide direct health care (eg, National Health Service in the United Kingdom). These guiding principles are listed in the Table; in addition, each area is discussed in more depth in the following sections as well as throughout this Special Issue of *Clinical Therapeutics*.

DISEASE KNOWLEDGE

When considering the creation of preventive interventions, it is essential to have robust data from natural history longitudinal cohorts (eg, registries) to help in the understanding of disease development and progression in their presymptomatic setting. Such data will allow for the formation of robust prediction models, as well as identify targets for prevention.

Identification of At-risk Individuals

Identifying at-risk individuals is a critically important step in the development of clinical trials, approval of preventive interventions, and ultimately in the implementation into clinical care. Specifically, it must be shown that individuals at risk for a future stage of disease that may be deemed more severe (eg, frank synovitis) can be accurately identified by using readily available methods such as blood-based biomarkers and, in the case of RA, potentially early symptoms of disease that are not yet clearly associated with tissue injury.

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Table. Guiding principles for gaining regulatory approval for prevention in rheumatoid arthritis.

Disease knowledge	Clear knowledge of early disease biology and progression (supported by data), and demonstrate the need and benefit of interventions in presymptomatic disease versus the current paradigm of treating symptomatic disease
Identification of at-risk individuals	Accurate and cost-effective screening to allow identification (with a high degree of confidence) of the appropriate population "at risk" in the presymptomatic setting and to have the knowledge and tools to monitor disease progression
Determination of appropriate outcomes to demonstrate success of preventive interventions	Proposal of acceptable end points for evidence generation in clinical trials (including surrogates)
Benefit to risk assessments: safety, efficacy, and health outcomes	Understanding the balance of benefits from screening and prevention against possible harms to health
Cost-effectiveness	Understanding the balance of costs of screening and prevention against improvements in financial outcomes that can include reduced work loss and perhaps less costly medications
Input from stakeholders	Stakeholders include individuals who are at risk for disease and in whom prevention would be implemented, clinicians, industry (including diagnostics and therapeutics), health care payers, and national agencies that provide guidance for prevention

DETERMINATION OF APPROPRIATE OUTCOMES TO SHOW SUCCESS OF PREVENTIVE INTERVENTIONS

Determining appropriate outcomes to show the success of preventive interventions is an essential point to discuss and develop alignment with regulatory agencies as well as other key stakeholders. Current prevention trials in RA are focusing on the primary outcome of preventing the development of classifiable RA. However, additional outcomes could include improved symptoms as measured through patient-recorded outcomes, improved biomarker profiles (eg, decreased autoantibody levels or decreased inflammation), and the first clinically apparent appearance of inflammatory arthritis even if not meeting full disease classification. In particular, given the long period of time that it may take for an individual who is at risk for future RA to develop fully classifiable disease, agreement on an intermediate outcome such as symptom improvement or biomarker change may lead to shorter, more feasible clinical trials. For example, in prevention trials of type 1 diabetes, there have been efforts to use as primary end points a delay or prevention to a next stage of disease even if that stage is not symptomatic diabetes.[6] Similar approaches can be considered in RA.

BENEFIT TO RISK ASSESSMENT: SAFETY, EFFICACY, AND HEALTH OUTCOMES

A key aspect to gaining broad approval for prevention is to determine the need for screening and prevention in a particular disease. In other words, is the fully established disease sufficiently severe and/or expensive to warrant preventive efforts? For example, one could argue that a relatively benign disease with an effective, low-risk and low-cost treatment for the symptomatic phase has limited need for prevention, particularly if the therapy involved might introduce new risks for the patient. For RA specifically, there is ample evidence for the severity of disease, and as such, the argument that it is a disease that warrants preventive efforts may be readily apparent; however, this is still an area to address with regulatory agencies. Furthermore, there is growing understanding that for individuals with RA, on balance, prevention is likely more preferable to acquiring disease then implementing treatment once disease has become clinically apparent.[7]

Beyond that, the safety and efficacy of specific interventions will need to be carefully studied within clinical trials for prevention and to form a key part of trial design and outcome assessments. Although screening for RA risk and prevention are in their early phases, there are some guidelines put forth already that can help inform approaches.[8] In addition, once preventive approaches are approved, further safety and efficacy monitoring can occur through safety and efficacy surveillance that may occur within individuals who have participated in clinical trials, as well as in postmarketing situations once interventions for RA prevention have been approved.[9] This action is important in RA prevention in which one will need to know how safe and efficacious an intervention is perhaps long after a trial has been completed. Furthermore, although the duration of an intervention that will be efficacious in RA prevention has yet to be determined, knowing how long a preventive treatment will be needed has important meaning in terms of long-term safety. In particular, if a preventive intervention needs to be lifelong, safety becomes more prominent than if an intervention is only needed for a short time and results in long-lasting improvements.

COST-EFFECTIVENESS

In today's health care environment, consideration must be given to the cost-effectiveness of prevention. Ideally, this information would comprise a broad understanding of cost-effectiveness that would include the overall impact on the economy and not just direct medical costs and would also take into account long-term health projections and productivity (eg, days missed from work by either the affected individual or caretaker, reductions in secondary complications that might not be seen for decades after the prevention/interception therapies, increased working years). Careful consideration, in advance, of how prevention can reduce near- and long-term costs will help prioritize opportunities and direct investment. This factor may also require novel business models that are more appropriate for prevention to be considered.

Input From Stakeholders

Ongoing and early dialogue with all the critical stakeholders, including regulators, industry, payers, clinicians, and individuals at risk for disease, is key to defining and encouraging an acceptable pathway for development in prevention. To be successful will require approaches that include engaging with regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency very early in clinical trial development. Such activities could also include engagement of rheumatology organizations such as the American College of Rheumatology and the European League Against Rheumatism. Notably, the latter organization has already developed task forces to evaluate factors related to RA prevention, especially around the area of nomenclature and symptom assessments.[10,11] Industry at both the therapeutic and diagnostic level as well as payers will also need to be an integral part of these communications, in large part to understand the underlying value proposition to ensure that novel therapeutics in this space are reimbursable and to achieve broad market access for those individuals affected. It will also be important to engage with at-risk individuals at both an individual level as well as through lay agencies such as the Arthritis Foundation in the United States and the National Rheumatoid Arthritis Society in the United Kingdom. This approach will help to assess individuals' preferences regarding prevention, which are critical to the success of clinical trials and implementation of prevention in clinical care. Potentially, many or all of these stakeholders could be engaged through the creation of multistakeholder consortia groups that may have a key role to help move forward critical elements to allow development in this area.

CONCLUSIONS

Although there are many challenges to developing clinical implementation of prevention in the pre-RA period, this proposition is an attractive option for stakeholders to consider. Results from the ongoing clinical trials in RA prevention, as well as careful consideration of each of the points related to prevention mentioned in this review, will help move the field closer to making RA prevention a clinical reality.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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